**Supplemental Digital Content**

# Effects of sedatives on sleep architecture measured with odds ratio product in critically ill patients

## Contents

**Additional methods details**

### *1. Inclusion-Exclusion criteria*

Twenty-five mechanically ventilated critically ill patients who were included in our two previous studies (S1, S2) to receive either propofol (n=12) or dexmedetomidine (n=13) during the night were re-analyzed. At the time of the studies all patients had been receiving mechanical ventilation for at least 48h, were hemodynamically stable without vasoactive drugs and ventilated on assisted modes of support through cuffed endotracheal or tracheostomy tubes. Exclusion criteria were: 1) administration of any sedative drugs over the last 24 h; 2) Glasgow coma scale less than 11; 3) acute physiology score portion of the APACHE II greater than 15; 4) presence of delirium at the time of the study, as defined by the confusion assessment method for ICU; 5) detectable plasma levels of sedative drugs (i.e., benzodiazepine, propofol) before the study; 6) history of epilepsy or any other neurological disease that may potentially have significant effect on the quality of sleep; 7) history of sleep apnea; and 8) ongoing sepsis. Analgesia with opioids was a reason of exclusion in propofol (S1), but not in the dexmedetomidine study, provided that there was no change in the dose throughout the study (S2). Additional exclusion criteria in the dexmedetomidine study were heart rate less than 50 $min^{-1}$, $2^{nd}$ or $3^{rd}$ degree atrioventricular block, severe liver failure (bilirubin >100 μmol/l) and use of centrally acting α-2 agonists or antagonists within 24 h before start of the study (S2).

### *2. Summary of the two previous studies methods*

In propofol study each patient was studied during two consecutive nights with or without sedation with propofol in a random order (S1). In dexmedetomidine study each patient was studied during three consecutive nights ($1^{st}$, $2^{nd}$, $3^{rd}$) and the night of

dexmedetomidine administration was preceded and followed by a night without sedation (S2). Since during the two nights without dexmedetomidine (1st and 3rd), patients' clinical status and sleep architecture with conventional criteria did not differ (S2), in the current study the first (without sedation) and second (with dexmedetomidine sedation) nights were analyzed.

With propofol a bolus of 0.01–0.05 mg/kg was given over 2 minutes at 10.00 p.m. followed by continuous infusion adjusted to maintain level 3 on the Ramsay scale (S1). With dexmedetomidine a loading dose of 0.5 μg/kg was given over 20 minutes at 9:00 pm, followed by continuous infusion to maintain level −1 to −2 on RASS (S2). Continuous infusion of propofol was stopped at 7.00 a.m. and of dexmedetomidine at 6:00 a.m. Apart from this time interval, the patients did not receive any sedation throughout the study. If there was need for sedation, as judged by the primary physician, the patient was withdrawn from the study. To prevent bias in propofol or dexmedetomidine administration, only two senior intensivists (C.A. and E.K.) were responsible for sedatives titration and did not have access to electroencephalogram. Noise, nursing, and other interventions were minimized during the nights of the study. In addition, during the nights, light was decreased to a minimum level that did not interfere with patients' assessment. Care was taken to ensure similar environmental conditions among the two study nights. In addition, the mode of ventilation and assist level remained unaltered during the study nights.

Propofol and dexmedetomidine were used and both sedatives have a very short-half half-life. In addition, both sedatives were given at relatively low doses to achieve light sedation. It is highly unlikely that in patients in whom the night without sedation followed the sedation night (only in some patients in propofol study), sleep is affected by sedation which has been stopped 15 hours earlier.

### *3. ORP analysis*

The method of calculating ORP was described in detail previously (S3). Briefly, fast Fourier transform was applied to consecutive non-overlapping 3-second epochs of EEG (C3/A2 and C4/A1) throughout each recording. For each 3-second epoch sum of powers is calculated in four frequency ranges: 0.33-2.33 Hz, 2.67-6.33 Hz, 7.0-14.0 Hz, and 14.3-35.0 Hz. Power in each range is assigned a rank (0 to 9) based on its decile within the range encountered in reference clinical PSG studies. The four ranks are concatenated in order of the frequency ranges to produce 10,000 four-digit labels (0000 to 9999) that describe the rank powers in the four frequency bands. The probability (0-100%) of any pattern occurring during arousals or in epochs manually scored wake was determined in development files by reference to a look-up table (S3). Probability is divided by 40 (% epochs scored wake in development files) resulting in a range from 0 (never occurs during wakefulness or in arousals) to 2.5 (never occurs during epochs scored asleep).

In conventional scoring sleep architecture is reported as the amount (or %) of time spent in five stages: wake, NREM stages N1-N3, and REM sleep with the amounts in NREM stages 1-3 reflecting time spent in progressively increasing sleep depth (S4). However, stages wake and N2 are not uniform in their appearance. Thus, the EEG in epochs scored wake can range from full wakefulness (wake pattern throughout the epoch) to having almost 15 seconds of sleep pattern within the epoch. Differences in wake patterns are particularly relevant in critically ill patients in view of their reported state of pathological wakefulness, defined as behaviorally confirmed wakefulness characterized by an increase in slow-wave activity and a decrease in high-frequency activity (S5, S6). Likewise, the EEG in N2 can range from a pattern almost indistinguishable from N1, with the exception of the occasional spindle, to a pattern that is indistinguishable from stage N3, except that the duration of delta waves is just shy of 20% of the epoch (S3). ORP can distinguish these different

levels of stages wake and NREM sleep (S3). In the current study the % of time spent in 10 different ORP ranges (0.0-2.5) was determined in each subject and sleep architecture was characterized by the distribution of 30-second epochs with different ORP levels (0.0-0.25, 0.25-0.50, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5). The effects of sedation on sleep architecture were further characterized by the change in % of epochs with ORP <1.0 (corresponding to stable sleep), in unstable sleep (1.0-1.75, transitional state characterized by frequent wake intrusions), and wakefulness (ORP>1.75). A sedation-induced increase (>5%) in %ORP<1.0 was considered as an improvement in sleep quality.

### *4. Criteria for identifying normal sleepers*

Normal sleepers (n=38) were selected from the Sleep Heart Health Study (S7, S8) and were used as controls in a previous study (S9). Selection Criteria for normal sleepers included: a) Total recording time >6.0 hours, b) Sleep efficiency >80%, c) Apnea-hypopnea-index< 5 $hr^{-1}$, d) No complaints of restless legs, e) No symptoms of insomnia.

### *5. Statistical analysis*

Continuous variables are reported as means and standard deviation. Normality was assessed visually by means of normal-probability plots. Categorical variables are compared using chi-square or Fisher exact test and continuous variables by one-way analysis of variance and paired and un-paired t-tests, as appropriate. Pearson correlation is used to determine the relation between average ORP in each decile and average log power in each frequency range (n=10 data points). The % of time spent in 10 different 30-sec. average ORP ranges (0.0-0.25, 0.25-0.50, 0.5-0.75, 0.75-1.0, 1.0-1.25, 1.25-1.5, 1.5-1.75, 1.75-2.0, 2.0-2.25, 2.25-2.5) is determined in each subject and differences in % representation in each ORP decile among groups were evaluated

by paired and unpaired t-test and one-way analysis of variance, followed by post-hoc Bonferroni test. In case of inequality of variances (Levene's test), Welch ANOVA and post-hoc Games-Howell test were used. Similar analysis was performed in % of 30 sec epochs with ORP<1.0, 1.0-1.75 and >1.75. A two-tailed p value of <0.05 was considered significant and adjusted, if needed, for multiple comparisons with Bonferroni correction. We used IBM SPSS-Statistics for Windows v.25 (Armonk, NY, USA) for analysis.

**Additional results**

***1. General***

ORP analysis was not feasible in two patients from dexmedetomidine study and one normal sleeper. Therefore, 23 patients (12 with and without propofol and 11 with and without dexmedetomidine) and 37 normal sleepers were analyzed. Patients characteristics did not differ between the two studies (Table S1)

Most patients were studied several days after the acute illness and therefore had minimal analgesic requirements, at least for opioids. Only two patients were on continuous i.v. remifentanil at a low dose (0.05 mcg/Kg/min). In these two patients, remifentanil had been stopped at least three days before the study. One patient in the dexmedetomidine study was on transdermal fentanyl for pain control. By study design (S2) the dose of fentanyl was constant throughout the study.

As for other medications that could potentially affect sleep quality, 7 patients had received either antidepressant for depression control or mood stabilization (4 patients) or antipsychotic (quetiapine or haloperidol, 3 patients) for delirium treatment. One patient had received haloperidol.

The mean±SD dose of propofol used to maintain sedation 3 on Ramsay sedation scale was 0.88±0.35 mg/kg/h, and that of dexmedetomidine to maintain -1 to -2 on RASS 0.43±0.11 μg/kg/h.

Table S2 shows the results of conventional scoring in all patients (n=23), as well as in patients from propofol (n=12) and dexmedetomidine (n=11) study.

### *2. Propofol and Dexmedetomidine effects*

In the following Supplement section, we present the results of propofol and dexmedetomidine separately to determine if the effects of the two sedatives differ from each other.

*Sleep Architecture as Measured by 30-second ORP Values:*

Figure S2 and S3 shows distribution of 30-second epochs with different ORP values in normal sleepers and patients from propofol and dexmedetomidine study. In patients, at a given sedation status (off and on sedatives), the distribution in all deciles did not differ between the two studies. In both studies the patients without sedation were characterized by little time with ORP <1.0 and there was an excessive number of epochs with ORP>1.75 (Fig. S2 and S3). The distribution patterns differed significantly from normal sleepers.

Figures S4 shows the changes (due to sedation with propofol or dexmedetomidine) in % of 30-second epochs from baseline (% of epochs with - % of epochs without sedation) in each ORP decile (upper panel) and in different ORP ranges (lower panel) corresponding to stable sleep (ORP<1.0), traditional state (ORP 1.0-1.75) and wake (ORP>1.75). There was no significant difference between propofol and dexmedetomidine sedation. Compared to normal sleepers, both sedatives decreased the % of epochs with ORP>1.75 and increased the % of epochs with ORP<1.0.

*Power spectral patterns at different ORP levels*

Figure S5 shows the average changes in log power in different frequency ranges as ORP increased from the lowest to the highest decile in normal sleepers and patients receiving propofol or dexmedetomidine and table S3 shows frequency of positive and negative trends in individual participants. In normal sleepers Range 2 power decreased, while beta 1 and beta 2 powers increased, progressively in all subjects as ORP increased. Slow delta power decreased in most subjects while showing no significant trend in the rest. Alpha power showed no significant trends in most subjects while it changed in either direction in the remainder. Gamma power either increased or was unchanged as ORP increased.

The distribution of trajectories in all frequencies did not differ between patients receiving propofol and dexmedetomidine. With both sedatives, beta 1 and beta 2 powers increased significantly with ORP in all but one patient in whom the change was not significant (Table S3). This response pattern was similar to that of normal.

Independent on sedatives (propofol or dexmedetomidine) the clearest difference between sedated patients and normal sleepers was in the trajectory of Range 2 power. In the majority the response was akin to that of normal sleepers; power decreased significantly as ORP increased. However, in a substantial minority there was no significant trend. This response pattern did not differ between the two sedatives.

*Number of wake intrusions in epochs with different 30-second ORP ranges*

Table S3, bottom, shows the results of this analysis. As may be expected, in normal sleepers the number of wake intrusions per 30-second epoch increased progressively as 30-second ORP increased, being 0.00±0.1 per epoch when average ORP was between 0 and 0.25 and 9.77±0.11 per epoch for epochs >2.25. The same pattern was observed in patients sedated with propofol and dexmedetomidine study. At any given ORP range frequency of wake intrusions in sedated patients was

uniformly lower with many of the differences being significantly lower (Table S3, bottom). Differences from normal sleepers were, however, quantitatively very small. There was no difference between patients sedated with propofol and dexmedetomidine.

*Spindle Density*

Spindle density was extremely low relative to normal sleepers in patients receiving propofol or dexmedetomidine (Table S3, bottom). There was no difference in spindle density between propofol and dexmedetomidine study.

### *3. Patients in high %ORP>2.25 and low %ORP>2.5 group*

We choose %ORP>2.25 to characterize patients without sedation (%ORP>2.25 above and below median) for two reasons. Firstly, ORP in this range displayed the highest variability (range 0-67%) among patients and, secondly it has been shown that in critically ill patients %ORP>2.25 may affect weaning outcome (S6).

Median value of % ORP>2.25 was 3.05%. Eleven patients had <3.0% of epochs with ORP>2.25 (low %ORP>2.25 group, range 0.0%-2.7%), and 12 patients >3.05% of epochs with ORP >2.25 (high %ORP>2.25 group, range 3.05%-67%). The distribution of patients belonging to high %ORP>2.5 and low %ORP>2.5 group did not differ between propofol and dexmedetomidine study (Fisher exact test, p>0.05); six patients from propofol study and six from dexmedetomidine were included in high %ORP>2.5 group. The low %ORP>2.5 group includes six patients from propofol and five from dexmedetomidine study.

ORP was <1.0 in only 20% of high %ORP>2.5 group epochs and there was an excessive number of epochs with full wakefulness (>2.25). This distribution differed significantly from normal in all but two deciles (1.00-1.5), with frequency being lower in the first four deciles and higher in the upper four (Fig. S8). In the low %ORP>2.5 group 42% of epochs were in the intermediate 1.0-1.75 range, consistent

with a transitional state but commonly staged sleep. Distribution in this group was closer to normal with differences found in only three deciles (Figure S8).

The effect of administering sedatives varied with baseline status (Fig. S8, S9). Sedation caused a significant leftward shift, towards normal, in frequency distribution in both groups. However, correction was only partial in high %ORP>2.5 while being almost complete in low %ORP>2.5 group where no differences from normal subjects were found in all but the first decile (0-0.25).

Figure legends

Figure S1: Sleep Depth at different odds ratio product (ORP) deciles. Constructed from published data on relation between ORP and arousability (ref. S3, S10). The probability of epochs in different ORP deciles being scored wake or sleep by conventional criteria is shown in the upper inset with black (wake) and white (sleep) zones indicating agreement between two scorers, while grey zones indicate a split decision. Note that agreement between scorers is high when ORP is <1.0 or >1.75, while in the range 1.0-1.75 disagreement between scorers is common (see comments in the main text).

Figure S2: Distribution of 30-second epochs (mean±SD) with different odds ratio product (ORP) in normal sleepers (n=37) and in patients from propofol (n=12) and dexmedetomidine (n=11) study with and without sedation. Significant differences in each ORP decile between patients and normal sleepers are shown. At a given sedation status, there was no difference in any decile between propofol and dexmedetomidine study. *Significantly different from normal sleepers.

Figure S3: Distribution of 30-second epochs in three odds ratio product (ORP) ranges corresponding to stable sleep (ORP<1.0), unstable sleep (ORP 1.0-1.75) and wakefulness (ORP>1.75) in normal sleepers (n=37) and in patients from propofol (n=12) and dexmedetomidine (n=11) study with and without sedation. Significant differences in each ORP range between patients and normal sleepers are shown. At a given sedation status, there was no difference in any ORP range between propofol and dexmedetomidine study. *Significantly different from normal sleepers.

Figure S4: Mean±SD changes in % of 30-second epochs due to sedation with propofol and dexmedetomidine (% of epochs with - without sedation) in 10 deciles of ORP (upper panel) and in three different ORP ranges (lower panel), corresponding to

stable sleep (ORP<1.0), unstable sleep (ORP 1.0-1.75) and wakefulness (ORP>1.75). Notice that compared to without sedation, both sedatives (propofol and dexmedetomidine) decreased the % of epochs with ORP>1.75 (negative difference) and increased it with ORP<1.0 (positive difference). Independent on sedatives, the maximum average decrease and increase was observed at similar ORP; with sedation the maximum decrease from baseline occurred at ORP 2.25-2.50 (8.2% with propofol and 8.1% with dexmedetomidine), and the maximum increase at ORP 0.5-0.75 (7.6% with propofol and 8.9% with dexmedetomidine). There was no difference between changes induced by propofol and dexmedetomidine (unpaired t-test).

Figure S5: Changes in log power in different EEG frequency ranges (inset) as ORP increases from deep sleep (ORP near zero) to full wakefulness (ORP near 2.5) in normal sleepers and patients sedated either with propofol or with dexmedetomidine.

Figure S6: Individual distribution of 30-second epochs with different odds ratio product (ORP) in normal sleepers and in patients without and with sedation (either with propofol or dexmedetomidine).

Figure S7: Individual distribution of 30-second epochs with different odds ratio product (ORP) in four patients in whom without sedation, sleep efficiency (SE) was reported as 0% (absence of sleep). The number of the patients corresponds to Table S1. Black bars: Without sedation. Open bars: With sedation. In each patients SE without (No) and with sedation (Yes) is shown. Note the considerable variability in ORP distribution despite the report of no sleep with conventional scoring. In patient no. 5 without and with sedation (propofol) no sleep was reported (0% SE). In this patient ORP distribution clearly showed that sedation has a favorable effect on sleep, as indicated by a shift in sleep architecture to lower ORP (sedation increased %ORP<1.0 by 44.6%, see Table 1 in the main text). In patients no. 18, 19 and 21 sedation (with dexmedetomidine) increased SE to 22%, 65% and 51%, respectively. In these patients ORP distribution showed that sedation improved (no. 18), did not

affect (pat. no.19) or worsened sleep quality (pat. no. 21). See also table 1 in the main text.

Figure S8: Mean distribution of 30-second epochs with different odds ratio product (ORP) in normal sleepers and in high %ORP>2.25 and low %ORP>2.25 group with and without sedation. Note that in normal sleepers, epochs are predominantly in low ORP (moderate/deep sleep). In high %ORP>2.25 group the majority of epochs were distributed in high ORP (wakefulness), while in low %ORP>2.25 group in the middle ORP range (transitional state). Independent of baseline pattern (high or low) sedation caused a leftward shift with the effect being stronger when they were administered to patients with low %ORP>2.25. Significant differences in each ORP decile among groups are shown.

*, significantly different from normal sleepers; +, significantly different high vs. low %ORP>2.25 and high %ORP>2.25 on sedation vs. low %ORP>2.25 on sedation.

Fig. S9: Mean±SD changes in % of 30-second epochs due to sedation (% of epochs with - without sedation) in 10 deciles (upper panel) and in three different ORP ranges (lower panel) in high (blue line) and low %ORP>2.25 (red line) group. Notice the significantly different effects of sedation between the two groups. Sedation in patients of high %ORP>2.25 group decreased (negative difference) the % of epochs with ORP>1.5 and increased (positive difference) the % of epochs with ORP<1.5. Sedation in patients of low %ORP>2.25 unaltered the % of epochs with ORP>1.75 but decreased the % of epochs in the ORP range 1.0-1.75 and increased in the range 0.0-0.75. In both cases, however, the shift was towards deeper sleep.

*Significantly different from the change induced by sedation in high %ORP>2.25 group (unpaired t-test).

Figure S10: Example in one normal sleeper (panel A) and one patient in whom power in range 2 frequency increased paradoxically at high ORP values (points b, c, and d, Panel B). Panel C is a representative 30-second epoch from the normal sleeper

during stage wake (ORP 2.44) while panel D is an epoch from the patient (panel D) at a similar ORP (2.44). Values within each panel are absolute power (in $\mu V^2$) in the indicated frequency ranges in the 10 constituent 3-second epochs. Note that for approximately the same beta power, Range 2 power (fast delta + theta frequencies) was substantially higher in panel D.

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